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Low Fibrinogen Level: A Predisposing Factor for Venous Thromboembolic Events with Hormone Replacement Therapy

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Several studies have reported an association between hormone replacement therapy (HRT) in postmenopausal women and increased risk of idiopathic venous thromboembolic events (VTEs). Given the widespread use of HRT, it is important to identify factors that may predispose women on HRT to VTEs. To address this concern, we examined potential risk factors for VTEs in women assigned to HRT in the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, a three-year, double-blinded, placebo-controlled trial of 875 postmenopausal women designed to assess the effects of HRT on heart disease risk factors (HDL cholesterol, fibrinogen, blood pressure, and insulin). Women with a history of estrogen-associated VTEs were excluded from the trial. Ten women, all assigned to HRT, had a VTE during PEPI. Only baseline fibrinogen varied significantly between those who did (mean = 249.0 mg/dl) and did not (mean = 280.8 mg/dl) have a VTE while assigned to HRT ($P < 0.03$). Adjusting for covariates including age, smoking, body mass index, lipid levels, blood pressure, alcohol, exercise, and prior HRT or oral contraceptive use did not affect this finding. The significantly lower fibrinogen levels seen among women subsequently reporting VTEs may be a marker for a specific, but as yet undefined, coagulopathy that is magnified in the presence of exogenous hormones. However, larger studies are needed to confirm this finding. Am. J. Hematol. 61:271–273, 1999.

Key words: hormone replacement; fibrinogen; venous thrombosis

INTRODUCTION

Use of high-dose oral contraceptives (OCs) in premenopausal women increases the risk for venous thromboembolic events (VTEs). Additionally, observational studies [1–3] and one clinical trial [4] have reported that low-dose hormone replacement therapy (HRT) in postmenopausal women is associated with a 2- to 4-fold increased risk of idiopathic VTEs. Given the widespread use of HRT, it is important to identify factors that may predispose women to estrogen-associated VTEs. To address this concern, we examined potential risk factors for VTEs among women enrolled in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.

MATERIALS AND METHODS

PEPI was a 3 year, randomized, double-blind, placebo-controlled trial to assess the effect of HRT on selected heart disease risk factors in 875 postmenopausal women treated with either placebo ($n = 174$) or HRT ($n = 701$). Details of the study design have been previously published [5]. Women reporting a history of VTEs associated with estrogen use were excluded from the trial. The HRT regimens included unopposed estrogen (0.625 mg/day conjugated estrogens) and three combined estrogen/progestin regimens. Every participant gave informed written consent. Serum fibrinogen, a primary endpoint of PEPI, was measured at entry for all participants. Additional hemostasis factors, including antithrombin III activity, factor VII, protein C, and protein S were measured

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TABLE I. Baseline Characteristics of PEPI Participants by Treatment Group and VTE Occurrence†

Baseline characteristic	Non-cases/placebo (n = 174)	Non-cases/HRT (n = 691)	VTE cases/HRT (n = 10)	
	Mean (SE)	Mean (SE)	Mean (SE)	p-value*
Fibrinogen (mg/dl)[a,*]	288.3 (3.4)	277.3 (1.7)	245.9 (12.9)	<0.03
Age	55.9 (0.3)	56.1 (0.2)	55.8 (1.3)	0.8
BMI (kg/m^2)	26.4 (0.3)	25.9 (0.2)	26.7 (3.1)	0.6
Lp(a) (mg/dl)[a,b]	23.5 (3.0)	22.1 (1.4)	20.1 (11.4)	0.9
HDL-C (mg/dl)	61.4 (1.2)	63.0 (0.6)	60.7 (5.2)	0.7
LDL-C (mg/dl)	143.3 (2.1)	138.7 (1.0)	142.1 (7.4)	0.7
TG (mg/dl)[a]	93.1 (3.3)	91.9 (1.7)	111.2 (17.7)	0.2
Glucose (mg/dl)				
fasting	96.9 (0.7)	97.1 (0.4)	100.8 (3.1)	0.2
2-hr	112.9 (2.5)	114.2 (1.4)	107.1 (4.7)	0.2
Systolic BP (mmHg)	115.6 (1.1)	114.8 (0.5)	112.3 (4.9)	0.6
Diastolic BP (mmHg)	72.6 (0.6)	71.8 (0.3)	70.0 (2.4)	0.5
	n (%)	n (%)	n (%)	p-value**
Prior HRT use	86 (51)	397 (57)	7 (70)	0.5
Prior OC use	99 (57)	424 (61)	6 (60)	0.6
Smoked regularly	101 (58)	339 (49)	3 (30)	0.3
Aspirin (past 2 weeks)	65 (37)	284 (41)	6 (60)	0.3
Alcohol use[c]	114 (89)	476 (84)	8 (89)	0.8
Exercise (past 48 hr)	64 (37)	263 (38)	5 (50)	0.5

†Abbreviations: VTE, venous thromboembolic event; HRT, hormone replacement therapy; SE, standard error; BMI, body mass index; Lp, lipoprotein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglycerides; BP, blood pressure; OC, oral contraceptive.

*From Student's *t*-test, comparing VTE cases to non-cases assigned HRT.

**From Fisher's exact two-tailed test, comparing VTE cases to non-cases assigned HRT.

[a]Computed from log-transformed data.

[b]Data missing for 22 non-cases assigned HRT and 8 non-cases assigned placebo.

[c]12 or more drinks in the last 12 months; data missing for 1 VTE case, 127 non-cases assigned HRT, and 31 non-cases assigned placebo.

only in a subset of women and, therefore, were not included in our analysis.

VTEs in PEPI participants were identified through self-report and confirmed by medical records. Because diagnoses of VTEs were not standardized at the start of PEPI, the definition of VTE in this analysis was a confirmed report of pulmonary embolism (PE), deep vein thrombosis (DVT), or superficial phlebitis (SP).

The distributions of baseline characteristics in women who did and did not develop VTEs while on HRT during PEPI were compared. Differences were assessed using Student's t-tests for continuous variables and Fisher's exact two-tailed tests for categorical variables. Analysis of covariance was used to determine mean levels of continuous baseline characteristics associated with VTEs, adjusted for covariates. One non-case on HRT was excluded from analyses involving fibrinogen because of a physiologically implausible baseline level (5 mg/dl).

RESULTS AND DISCUSSION

During PEPI ten participants, all assigned to HRT, experienced a VTE: two with PE, two with DVT, and six with SP. Four of the VTEs occurred in the first year of the trial. No participant assigned to placebo reported a VTE and the risk of VTE did not vary by progestin used.

The combined rate of DVT and PE in the HRT-treated women was 1.96 (95% confidence interval 0.7–5.2) per 1,000 person-years. The overall age-adjusted incidence rate of DVT and PE among women in a population-based study was reported to be 1.1 per 1,000 [6]. Therefore, consistent with previous studies [1–3], PEPI participants assigned to HRT were at almost a 2-fold increased risk of DVT and PE compared to the general population.

The distributions of selected baseline characteristics in those who did and did not develop VTEs are shown in Table 1. Only one factor differed between those who did and did not have a VTE: baseline fibrinogen level. Women who experienced VTEs had a significantly lower mean fibrinogen level (249.0 mg/dl) than those who did not (280.8 mg/dl) ($P < 0.03$). Adjusting for covariates (e.g., age, BMI, lipid levels, blood pressure, smoking, alcohol, exercise, and prior HRT or OC use) did not alter this finding. During the trial, fibrinogen levels increased among placebo-treated women (approximately 10 mg/dl), while remaining stable in women assigned to HRT

[7]. However, change in fibrinogen level with HRT was not associated with subsequent risk of VTE.

The observation that fibrinogen levels were lower among VTE cases than among non-cases is puzzling given that women who experienced VTEs may be in a prehypercoaguable state. However, lower fibrinogen levels have been associated with small blood clots in individuals with an acquired coagulation disorder, disseminated intravascular coagulation [8]. Thus, the lower levels of fibrinogen observed among women subsequently experiencing VTEs may be a marker for a specific but as yet undefined coagulopathy whose effects may be magnified in the presence of exogenous hormones.

It is possible that our finding of lower fibrinogen levels among VTE cases was a chance finding, as we have a small number of VTEs. However, given the direct and indirect effects that estrogen may have on hemostatic function [9], it is important to determine if there is a real association between low fibrinogen levels, HRT, and VTE occurrence. Additional research is needed to elucidate the effect of hormones on the complex process of thrombosis as well as on factors that may predispose women to estrogen-associated VTEs.

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